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NOVEL ROUTE FOR OBTAINING ISOMERIC BENZO[*b*]THIOPHENOINDOLES

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We describe a novel route for synthesis of benzo[b]thiopheno[2,3-e]- and benzo[b]thiopheno[3,2-f]-indoles. As the starting compounds, we used the corresponding annelated isatins obtained by the Sandmeyer reaction. We have established that reduction of the latter to the corresponding unsubstituted benzo[b]thiophenoindoles depends both on the nature of the substituent and on the reaction conditions.

Keywords: benzothiophenoindole, dibenzothiophene, isatin, indole.

The isomeric dioxodihydro-1H-benzo[*b*]furanoindoles we synthesized by the Sandmeyer reaction in [1] are quite applicable for synthesis of unsubstituted indole-containing tetracyclic systems and their hydroxy derivatives with different couplings of the pyrrole ring relative to the original tricyclic system. In continuing our research in this direction, we felt it would be interesting to carry out the analogous reaction for isomeric dioxodihydro-1H-benzo[*b*]thiophenoindoles, also obtained by the Sandmeyer reaction.

By reaction of 3-aminodibenzothiophene (**1**) with chloral hydrate and hydroxylamine hydrochloride, followed by cyclization of 3-(isonitrosoacetamido)dibenzothiophene (**2**) under Sandmeyer reaction conditions [2, 3], we obtained a mixture of the corresponding isomeric annelated isatins **3, 4**. We used sulfuric acid as the cyclizing agent.

We separated the isomers by subsequent treatment of an alkaline solution of a mixture of compounds **3, 4** with acetic acid to pH 3, and after removal of the precipitating crystals, by acidification of the filtrate with hydrochloric acid to pH 1. Compound **3** (60%) precipitates first, then compound **4** (25%). We have established that compounds **3** and **4** can be converted to the corresponding benzo[*b*]thiophenoindoles **5** and **6**, the yield of which depends both on the nature of the reducing agent and on the reaction conditions. Thus on reduction of isatins **3** and **4** by lithium aluminum hydride in absolute pyridine or sodium borohydride in 2-propanol, a mixture is formed consisting of the corresponding hydroxybenzo[*b*]thiophenoindoles **7** and **8**, an insignificant amount of unsubstituted benzo[*b*]thiophenoindoles **5** and **6** and unreacted compounds **3** and **4**. The use of diborane as the reducing agent in THF results in synthesis of unsubstituted benzo[*b*]thiopheno[2,3-*e*]indole (**5**) and benzo[*b*]thiopheno[3,2-*f*]indole (**6**) in acceptable yields (Scheme 1).

In the IR spectrum of compound **2**, we observe an absorption band for the C=O group in the 1690 cm^{-1} region, and an absorption band at 3300 cm^{-1} indicates the presence of an NH group. The absorption bands for the C=O group in the IR spectra of compounds **3** (1710 cm^{-1}) and **4** (1700 cm^{-1}) are close to the corresponding band in isatin. Unfortunately, due to the poor solubility of compounds **3** and **4** in ethanol, we could not take their UV spectra.

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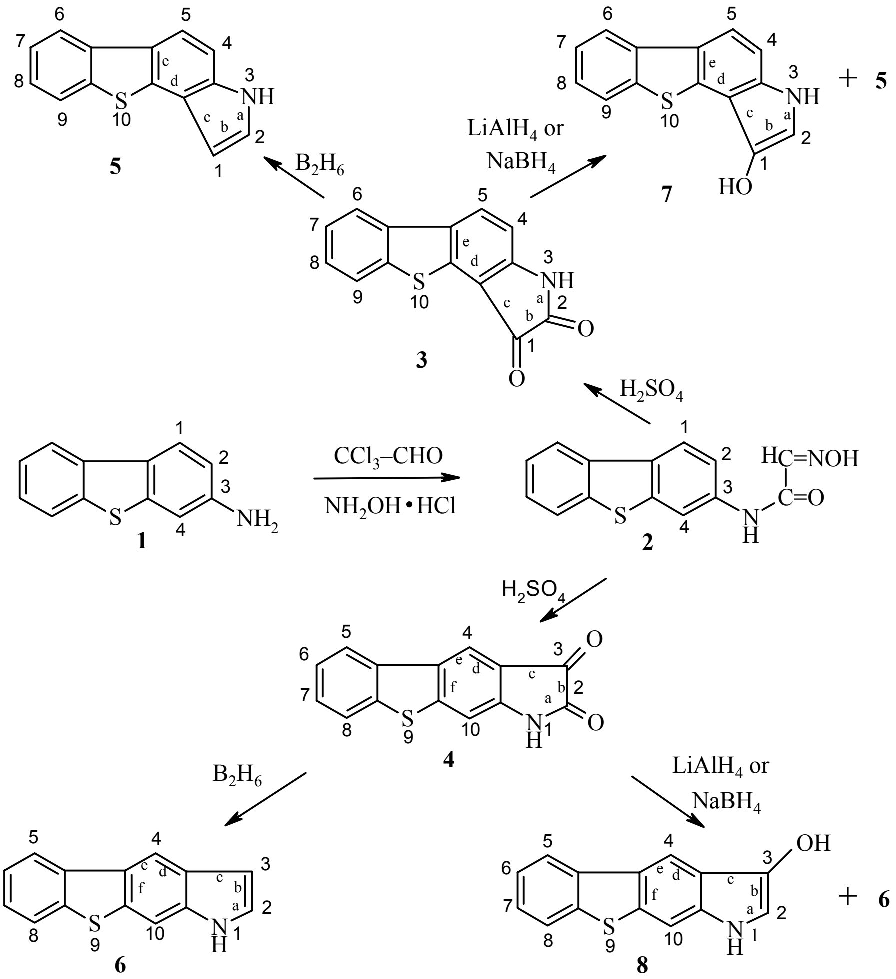
Scheme 1



We assigned the ^{1}H NMR signals (Table 1) for compounds **3** and **4** based on the differences in the multiplicity of the signals for the indole portion of the molecules: the presence of the spectrum for an AB system with spin–spin coupling constants that are typical of *ortho* protons in the case of angular coupling of the rings (compounds **3**), or two signals from the weakly interacting π-protons in the case of a linear molecule (compound **4**).

In the mass spectra of isomeric annelated isatins **3** and **4**, we observe an intense peak for the molecular ion [M$^+$] with *m*/*z* 253; and the nature of the further fragmentation, confirmed by the metastable transitions, does not contradict the proposed structures.

In the IR spectra of compounds **5** and **6**, there are absorption bands for the NH group at 3390 cm^{-1} and 3400 cm^{-1} respectively. The UV spectra of compounds **5** and **6** are similar to the spectra of compounds we obtained previously by the Fischer reaction. Mixed samples of compounds **5** and **6** with known compounds obtained by the Fischer reaction [5] did not result in depression of the melting point.

In the IR spectra of compounds **7** and **8** there is an absorption band typical of the OH group in the region 3490-3510 cm^{-1} and 3440-3490 cm^{-1} respectively, and the UV spectrum resembles the spectrum of indole. In the ^{1}H NMR spectra of compounds **7** and **8**, there is a narrow singlet for the proton of the OH group at 8.19 ppm and 8.13 ppm respectively.

TABLE. ^{1}H NMR Spectrum of the Compounds **3-8**

Compound	Solvent	δ, ppm										*J*, Hz
		NH	2-H	3-H/1-H	10-H	8-H/9-H	7-H/8-H	6-H/7-H	5-H/6-H	4-H/5-H	4-H	
3	DMSO-d_6	11.65	—	—	—	7.72	7.66	7.48	8.19	8.33	6.93	$J_{4,5} = 8.1$; $J_{6,7} = 7.2$; $J_{7,8} = 7.3$; $J_{8,9} = 8.3$
4	DMSO-d_6	11.22	—	—	7.11	7.66	7.49	7.40	8.12	8.37	—	$J_{4,10} = 0.8$; $J_{6,7} = 7.7$; $J_{7,8} = 8.1$; $J_{5,6} = 7.3$
5	Acetone-d_6	10.61	7.54	7.22	—	7.63	7.40	7.39	8.52	7.62	7.62	$J_{1,2} = 2.2$; $J_{1,3} = 1.9$; $J_{2,3} = 3.0$; $J_{1,4} = 0.5$; $J_{4,5} = 8.4$
6	DMSO-d_6	10.40	~7.36	6.53	8.27	7.50	7.35	7.79	8.17	7.99	—	$J_{1,2} = 2.4$; $J_{1,3} = 2.0$; $J_{2,3} = 3.0$; $J_{4,10} = 0.7$; $J_{4,5} = 8.4$; $J_{6,7} = 7.5$
7	Acetone-d_6	10.15	~7.15	8.19*	—	7.68	7.38	7.41	8.20	8.31	7.04	$J_{7,8} = 7.3$; $J_{8,9} = 8.0$; $J_{4,10} = 0.9$; $J_{6,7} = 7.4$
8	Acetone-d_6	10.21	~7.22	8.13*	7.76	7.64	7.34	7.22	8.17	8.36	—	$J_{5,6} \sim J_{7,8} = 7.5$

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* Proton of the hydroxyl group.

The method we propose considerably decreases the number of steps for synthesis of heterocyclic systems **5** and **6** compared with obtaining them by the Fischer reaction. As a result of the reduction, we isolated and characterized the 1- and 3-hydroxy derivatives **7** and **8**, which have not been described previously and which are of interest from a pharmacological viewpoint [4].

EXPERIMENTAL

The UV spectra were measured on a Specord UV-vis (in ethanol, in cuvetts with path length 1 cm). The IR spectra were taken on a UR-20 spectrophotometer (in vaseline oil). The ^{1}H NMR spectra were recorded on a Varian CFT-20 spectrometer with operating frequency 80 MHz (internal standard, TMS). The mass spectra were taken on an MKh-1303 with direct injection of the sample into the ion source, cathode emission current 1.5 μA, ionizing potential 50 eV.

3-(Isonitrosoacetamido)dibenzothiophene (2). Crystalline $Na_2SO_4 \cdot 10H_2O$ (260 g, 0.8 mol), 3-aminodibenzothiophene **1** (19.9 g, 0.1 mol) dissolved in hot water (3 l) with addition of conc. HCl (20 ml), and hydroxylamine hydrochloride (22.3 g, 0.32 mol) dissolved in water (100 ml) were added successively to a solution of chloral hydrate (16.5 g, 0.1 mol) in water (240 ml). The mixture was rapidly heated to boiling and then boiled with constant stirring for 2 h, after which the reaction mass was cooled with water. The precipitated crystals of compound **2** were filtered out, carefully washed with water, and dried. Yield 24.3 g (90%); mp 213-215°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1690 (C=O). UV spectrum, λ_{max}, nm (log ε): 235 (4.41), 265 (4.10), 285 (4.15), 333 (4.05), 350 (4.00). Found, %: C 62.0; H 4.0; N 10.4; S 11.6. $C_{14}H_{10}N_2O_2S$. Calculated, %: C 62.2; H 3.7; N 10.3; S 11.9.

1,2-Dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[2,3-*e*]indole (3) and 2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[3,2-*f*]indole (4). Compound **2** (13.5 g, 0.05 mol) were added in small portions with constant stirring at 50°C to a solution of 75% H_2SO_4 (14.7 g, 0.3 mol). The reaction mixture was heated for 1 h at 80°C, then was slowly cooled down and poured into a 10-12-fold amount of ice. After 1 h, the precipitate was filtered out and washed with water. The crude product was suspended in a 5-fold amount of hot water and a 40% NaOH solution was added with stirring until the suspension had completely dissolved. A 12% HCl solution was carefully added until precipitation began. The precipitate was filtered out and discarded. Acetic acid was carefully added to the filtrate until pH 3 was reached, and it was allowed to stand for 2.5 h. The precipitate was again filtered out, carefully washed with water, and dried. Obtained 7.59 g of compound **3**. Yield 60%; mp 312-314°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 3260 (NH···O=C), 1710 (C=O). Found, %: C 66.2; H 3.0; N 5.2. $C_{14}H_7NO_2S$. Calculated, %: C 66.4; H 2.7; N 5.5.

After separation of the product **3**, the filtrate was acidified with conc. HCl to pH 1 and allowed to stand for 1 h. The precipitated crystals were filtered off, carefully washed with water until they tested neutral, and dried. Obtained 2.5 g of compound **4**. Yield 25%; mp 294-296°C. IR spectrum, ν, cm^{-1}: 3390 (NH), 3250 (NH···O=C), 1700 (C=O). Found, %: C 66.1; H 2.8; N 5.8. $C_{14}H_7NO_2S$. Calculated, %: C 66.4; H 2.7; N 5.5.

Benzo[*b*]thiopheno[2,3-*e*]indole (5). A solution of diborane (1.7 g, 0.06 mol) (obtained *in situ* from sodium borohydride and boron trifluoride etherate) was added dropwise with stirring to a solution of compound **3** (2.53 g, 0.01 mol) in abs. THF (2.5 ml) at -78°C. The mixture was held for 30 h at 0°C. The reaction mixture was poured into water (1.5 l) that had been weakly acidified with HCl, and the reaction product was extracted with ether. The extract was washed with water and dried over Na_2SO_4. After distilling off the solvent, the product was purified on a silica gel column (diethyl ether–petroleum ether, 1:5). Obtained 1.34 g of compound **5**. Yield 70%; mp 138-140°C. IR spectrum, ν, cm^{-1}: 3380 (NH). UV spectrum, λ_{max}, nm (log ε): 255 (5.13), 297 (4.45), 310 (4.45), 325 (4.25). Found, %: C 75.1; H 3.8; N 6.1; S 14.0. $C_{14}H_9NOS$. Calculated, %: C 75.3; H 4.0; N 6.3; S 14.3.

Benzo[*b*]thiopheno[3,2-*f*]indole (6) was obtained similarly to compound **5** from **4** as the starting material. Yield 60%; mp 190-192°C. IR spectrum, ν, cm^{-1}: 3410 (NH). UV spectrum, λ_{max}, nm (log ε): 208 (4.51), 245 (4.80), 252 (4.81), 270 (4.21), 295 (4.18), 312 (4.50), 310 (4.40). Found, %: C 75.4; H 4.2; N 6.2; S 14.3. $C_{14}H_9NS$. Calculated, %: C 75.3; H 4.0; N 6.3; S 14.3.

1-Hydroxy-1H-benzo[*b*]thiopheno[2,3-*e*]indole (7) and 3-Hydroxy-1H-benzo[*b*]thiopheno[3,2-*f*]-indole (8). A. Lithium aluminum hydride (2.4 g, 0.09 mol) was mixed (with cooling) with absolute pyridine (240 ml), and dried compound **3** (5.1 g, 0.02 mol) was added in portions with stirring so that the temperature of the reaction medium did not go above 25°C. After 8 hours of stirring, water (20 ml) and then a solution of tartaric acid (240 g) in water (960 ml) were added dropwise. The product was extracted with ether, the extract was washed with a dilute solution of tartaric acid and water and then dried over Na_2SO_4, and the solvent was distilled off. The product was purified on a silica gel column (diethyl ether–hexane, 1:3). Obtained 1.9 g of gradually crystallizing compound **7**. Yield 40%; mp 215-216°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 3490-3500 (OH). UV spectrum, λ_{max}, nm (log ε): 235 (4.45), 260 (4.70), 275 (4.65), 310 (4.40). Found, %: C 70.4; H 4.0; N 6.0; S 13.6. $C_{14}H_9NOS$. Calculated, %: C 70.2; H 3.7; N 5.8; S 13.4.

Compound 8 was obtained similarly from annelated isatin **4**. Yield 30%; mp 180-194°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 3490-3510 (OH). UV spectrum, λ_{max}, nm (log ε): 230 (4.40), 260 (4.90), 335 (4.15). Found, %: C 70.2; H 3.8; N 6.1; S 13.2. $C_{14}H_9NOS$. Calculated, %: C 70.2; H 3.7; N 5.8; S 13.4.

B. Compound **3** (2.5 g, 0.01 mol) was added to a solution of sodium borohydride (1.1 g, 0.04 mol) in 2-propanol (50 ml) at ~20°C. The mixture was heated up to 50°C for 3 h and allowed to stand overnight at ~20°C. Then dilute hydrochloric acid was carefully added until evolution of hydrogen stopped. The product was extracted from the reaction mixture with small portions of ether. The ether extract was carefully washed with water and dried over Na_2SO_4. The solvent was distilled off. The product **7** was purified on a silica gel column (diethyl ether–hexane, 1:3). Yield 0.8 g (35%).

Mixed samples of compounds **7** and **8** obtained by methods A and B did not result in depression of the melting point.

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